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EXPERIMENTAL STUDIES

Barium-Induced Nondriven Action Potentials as a Model of Triggered Potentials From Early Afterdepolarizations: Significance of Slow Channel Activity and Differing Effects of Quinidine and Amiodarone

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Triggered activity due to early afterdepolarizations in the context of prolonged repolarization is believed to cause torsade de pointes. The nature of such triggered activity is not clearly defined. Spontaneous action potentials developing from depolarized membrane potentials were studied in canine Purkinje fibers with use of a standard microelectrode technique. Action potentials due to abnormal automaticity and additional depolarizations developing over the repolarization phase were induced by 5 m*M* barium superfusion. These action potentials were abolished by 1.0×10^{-5} *M* verapamil and by calcium-free solution, whereas action potential amplitude ($\dot{V}_{max}$) and spontaneous firing frequency were markedly enhanced by 2.0×10^{-6} *M* isoproterenol. High calcium solution shortened the action potential duration and precluded additional depolarizations.

Quinidine, 1.0×10^{-5} *M*, reduced action potential amplitude (6.9 ± 1.8 %: $p < 0.01$), $\dot{V}_{max}$ (15.7 ± 4.0 %; $p < 0.05$) and spontaneous firing frequency (18.5 ± 2.1 %; $p < 0.01$), but it increased action potential duration measured at −40 mV (19.1 ± 5.9 %; $p < 0.01$), which produced additional depolarizations. Amiodarone, 5.0×10^{-5} *M*, reduced action potential amplitude (23.4 ± 3.6 %; $p < 0.01$), $\dot{V}_{max}$ (44.6 ± 3.9 %; $p < 0.01$) and spontaneous firing frequency (41.9 ± 5.1 %; $p < 0.01$). Amiodarone obviated the development of additional depolarizations without effect on action potential duration.

The data indicate that 1) triggered potentials from early afterdepolarizations are slow calcium channel dependent; 2) the duration of the plateau phase mediates the development of triggered activity from low membrane potential; 3) the effects on plateau currents but not direct effects on triggered potentials may contribute to the arrhythmogenic action of quinidine; and 4) the known associated slow channel blocking property of amiodarone may account for the low incidence of torsade de pointes during long-term amiodarone therapy.

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Polymorphous ventricular arrhythmia associated with a long QT interval forms a distinctive category of cardiac arrhythmia designated "torsade de pointes." This type of arrhythmia occurs commonly in association with hypokalemia or bradycardia, or both (1). Recently, Brachmann et al. (2) demonstrated that cesium at concentrations that could initiate ventricular arrhythmias in association with a long QT interval in intact dogs produced triggered activity from early afterdepolarizations in isolated preparations. They postulated that such triggered potentials from early afterdepolarizations might be one of the cellular electrophysiologic mechanisms for the development of this type of arrhythmia. Indeed, early afterdepolarizations and triggered activity have been demonstrated to occur in isolated cardiac tissues by other agents also known to cause torsade de pointes. Such agents included quinidine (3), N-acetylprocainamide (4) and sotalol (5).

More direct evidence of a link between triggered potentials from early afterdepolarizations and ventricular arrhythmias has been provided from the recordings of monophasic action potentials (6,7). Early afterdepolarizations have been defined by Cranefield (8) as afterpotentials that appear over phase 2 or phase 3 of an action potential. Therefore, trig-

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gered activity due to early afterdepolarizations occurs in the context of delayed repolarization when the membrane potential is maintained at a less negative potential. A number of studies (9–12) have shown that cardiac tissues develop spontaneous action potentials when they are subjected to electrical or pharmacologic maneuvers that produce low membrane potentials. The propensity in various cardiac tissues, especially in Purkinje fibers (7), to give rise to nondriven action potentials from depolarized membrane potentials may form the basis of arrhythmias in the setting of prolonged repolarization.

The present study was designed to investigate this possibility in isolated canine Purkinje fibers. Barium was used to induce such action potentials because it is known to depolarize the resting potential and to initiate spontaneous action potentials (13–15). Electrophysiologic features of these action potentials and effects of two major antiarrhythmic agents (quinidine and amiodarone), each having distinctive electrophysiologic properties relative to the genesis of torsade de pointes, were investigated.

Methods

Experimental preparation. Mongrel dogs of either gender (weighing 15 to 25 kg) were anesthetized with sodium pentobarbital (30 mg/kg body weight intravenously) and the heart was rapidly removed through a thoracotomy and dissected in cool oxygenated Tyrode's solution. Purkinje fibers were obtained from both ventricles. The preparations were fixed in a tissue bath and superfused with Tyrode's solution aerated with 95% oxygen and 5% carbon dioxide. The volume of the tissue bath was 3.0 ml and the turnover time in changing the solution was about 5 min. The composition of the Tyrode's solution was as follows (in m*M*): sodium chloride (NaCl) 130.0, potassium chloride (KCl) 4.0, calcium chloride ($CaCl_2$) 1.8, magnesium sulfate ($MgSO_4$) 0.5, monosodium phosphate (NaH_2PO_4) 1.8, sodium bicarbonate ($NaHCO_3$) 18.0, and dextrose 5.5; the pH range of the solution was 7.25 to 7.35. The experiments were carried out at 35.5° to 36.5°C; however, during each experiment the temperature was monitored and the variation was kept to $<\pm 0.2$°C.

Recording and protocol. Transmembrane potentials were recorded through two glass microelectrodes filled with 3 *M* KCl, one intracellularly and the other extracellularly, placed close together. The upstroke of the action potential was electronically differentiated to measure the maximal upstroke velocity ($\dot{V}_{max}$). Preparations were stimulated through bipolar extracellular electrodes (Teflon-coated silver wire) with rectangular pulses 1 to 2 ms in duration. After 1 h of initial equilibration continuously stimulated at 1 Hz, the membrane potentials were recorded. Preparations with membrane potentials that satisfied all of the following criteria were retained for further experiments: resting potential negative to −80 mV, action potential amplitude >115 mV, $\dot{V}_{max}$ >400 V/s, and action potential duration >250 ms measured at −40 mV. Thereafter, the solution was switched to the Tyrode's solution containing 5 m*M* barium chloride. External stimulation was discontinued when abnormal automaticity developed or the preparation could no longer respond to the stimulation. If the developed abnormal automaticity showed constant firing for ≥30 min, control data were recorded before proceeding to the next step of the study. A single continuous microelectrode impalement was maintained throughout each experiment.

Superfusion media. Barium chloride was dissolved in deionized water and diluted with Tyrode's solution to achieve a final concentration of 5 m*M* (control solution). Test solutions each containing high levels of calcium, verapamil, isoproterenol and quinidine were made by adding adequate volume of stock solution of the respective chemical to the control solution. When the test solution of amiodarone was made, bovine albumin was added to the control solution to achieve 1.0% albumin concentration. Then a small amount of ethanol solution containing amiodarone to achieve 5.0×10^{-5} *M* was added slowly to half of the solution containing 1.0% albumin. The test solution of amiodarone was made immediately before each experiment because visible precipitation was usually evident in 1 or 2 h. Another half of the solution was used to wash out amiodarone. Calcium-free solution was made by removing $CaCl_2$ from the Tyrode's solution, then adequate volume of stock solution of barium chloride was added to achieve a concentration of 5 m*M*.

Terms and statistical analysis. The term "early afterdepolarization" is used restrictively to describe afterpotentials that produce delay in repolarization in which the net current is zero or still outward. And "positive" depolarizations caused by inward currents are regarded as triggered potentials due to triggered activity. Values were expressed as the mean values ± SE. Student's *t* test (two-tailed) was used to make statistical comparisons and p values <0.05 were considered to indicate a significant difference.

Results

Characteristics of barium-induced nondriven action potentials (Fig. 1 and 2). The first series of changes produced by barium superfusion in the membrane potentials driven at 1 Hz were characterized by an increase in the action potential duration, disappearance of the rapid repolarization in phase 1 and acceleration of the rate of diastolic depolarization (Fig. 1). The resting potential remained unchanged or was hyperpolarized slightly. During this initial phase, triggered activity due to early afterdepolarizations could be easily initiated with or without slowing the stimulation frequency. Usually triggered potentials were observed at low membrane potential (around −20 mV) or at high membrane potential (around

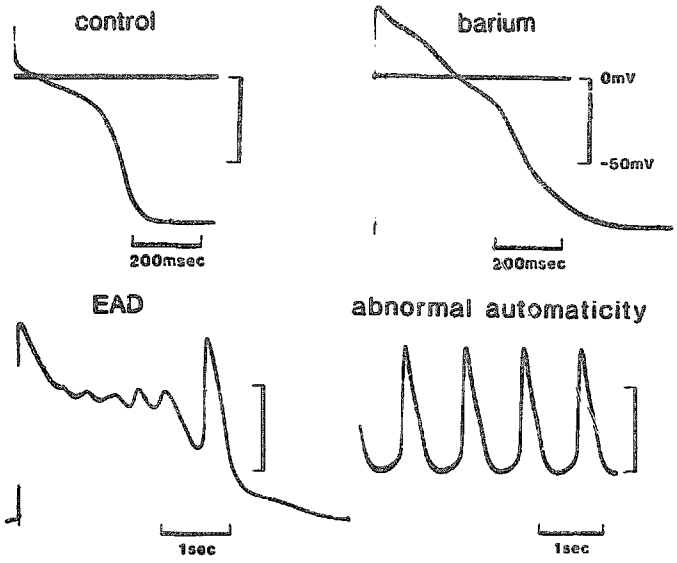

Figure 1. Characteristics of barium-induced nondriven action potentials. *Control*: An action potential in normal Tyrode's solution driven at 1.0 Hz. *Barium*: Early phase of a superfusion with "control solution" (i.e., Tyrode's solution containing 5 m*M* barium). The preparation was still driven at 1.0 Hz. *EAD*: Triggered activity due to early afterdepolarizations (EAD) developed by reducing the stimulation frequency. Note the development of triggered potentials at a low membrane potential as well as at a high membrane potential. *Abnormal automaticity*: Action potentials due to abnormal automaticity. All action potentials were recorded from the same preparation.

−50 mV), or both. Thereafter, the resting potential gradually shifted to a voltage between −50 mV and −60 mV with development of spontaneous firing of action potentials (Fig. 1). The characteristics of action potentials due to abnormal automaticity were similar to those of triggered potentials from high membrane potential observed in the early phase of the same preparation. Preparations that demonstrated ab-

Table 1. Action Potentials Due to Abnormal Automaticity Induced by Barium

MDP (−mV)	AMP (mV)	$\dot{V}_{max}$ (V/s)	APD_{-40} (ms)	Frequency (beats/min)
55.3 ± 0.6	75.7 ± 1.1	12.2 ± 0.6	369.4 ± 7.7	61.1 ± 1.7

AMP = ampitude of an action potential; APD_{-40} = action potential duration measured at −40 mV; MDP = maximal diastolic potential; $\dot{V}_{max}$ = maximal upstroke velocity of an action potential. Values are mean values ± SEM (n = 46).

normal automaticity with constant firing of regular action potentials (e.g., the preparation shown in Figure 1) were designated as the "regular group."

The average features of the regular action potentials are summarized in Table 1. These preparations were used to study the effects of interventions on action potentials due to abnormal automaticity. However, sometimes additional depolarizations developed interrupting the repolarization of these action potentials (Fig. 2). Such additional depolarizations tended to develop from action potentials with longer action potential duration. Even transient prolongation of the duration of an action potential was observed before the development of additional depolarizations (Fig. 2a). These depolarizations developed from any level of membrane potentials negative to −10 mV. It appeared that the more negative the takeoff potential, the higher the amplitude of the depolarization (Fig. 2b). Additional depolarizations that appeared from less negative potential showed an oscillatory nature (Fig. 2c). Preparations in which these additional depolarizations occurred only occasionally or transiently in the regular action potentials were included in the "regular group" and measurements were obtained while they showed normal repolarization constantly.

In some preparations, an interruption of the repolariza-

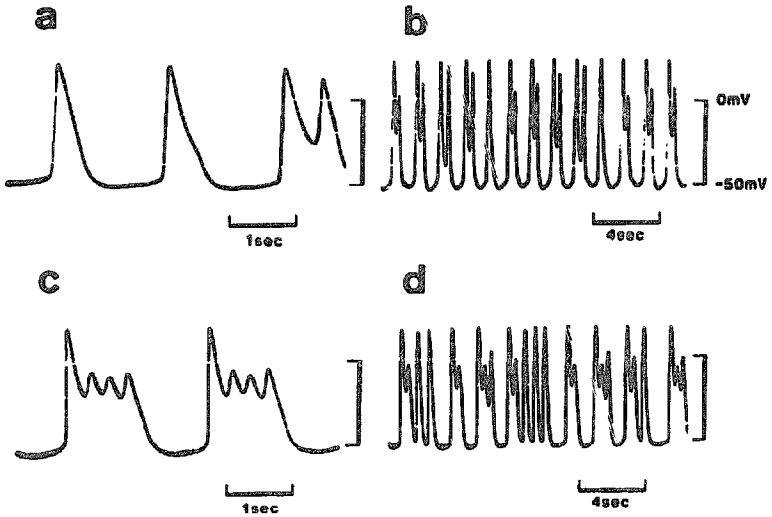

Figure 2. Additional depolarizations developing over the repolarization phase (early afterdepolarizations from low membrane potential). **a**, Action potentials due to abnormal automaticity in control solution. Note the development of an additional depolarization in the third action potential preceded by transient prolongation of the repolarization phase in the second action potential. **b**, Additional depolarizations with various takeoff potentials. The more negative the takeoff potential, the higher the amplitude of additional depolarization. **c**, Additional depolarizations from a lower membrane potential exhibiting an oscillatory nature. **d**, Frequent appearance of multiple additional depolarizations in a preparation categorized into the "irregular group."

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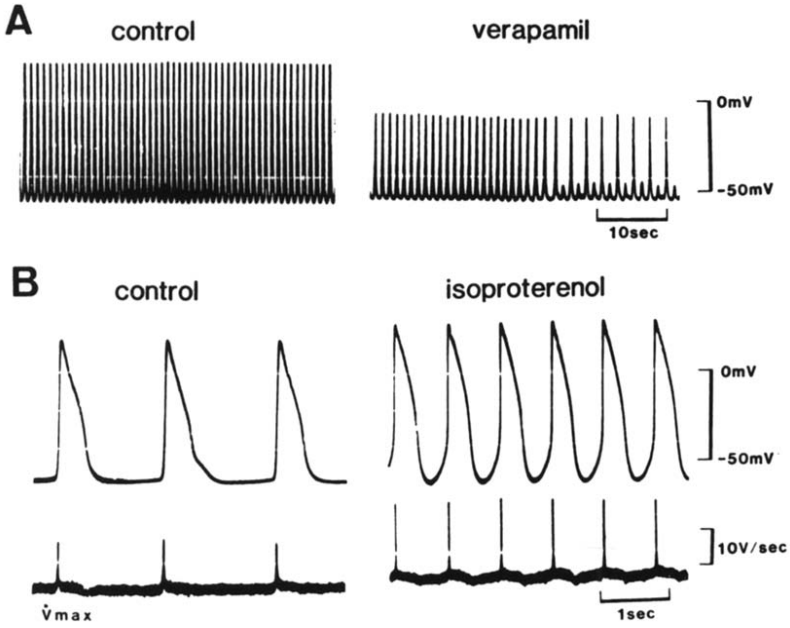

Figure 3. Effects of verapamil and isoproterenol on action potentials. A, *Control*: Action potentials due to abnormal automaticity in control solution. *Verapamil*: Effects of verapamil at 1.0×10^{-5} *M*. Note the marked decrease in action potential amplitude and the 2:1 block in the later phase. Action potentials totally disappeared soon after this recording. B, *Control*: Action potentials due to abnormal automaticity and their $\dot{V}_{max}$ in control solution. *Isoproterenol*: Effects of isoproterenol at 2.0×10^{-6} *M*. Note the marked enhancement of amplitude and $\dot{V}_{max}$ of the action potential as well as of the firing frequency.

tion phase by additional depolarizations occurred consistently in almost all action potentials. Even multiple additional depolarizations frequently appeared in such preparations (Fig. 2d). These preparations were designated as representing the "irregular group" and were used to study the effects of interventions on additional depolarizations. Preliminary experiments on four preparations belonging to the "regular group" revealed that statistically significant change in variables of the action potential did not develop even after 4 h. Three preparations from the "irregular group" showed a constant appearance of additional depolarizations for >4 h.

Effects of verapamil, isoproterenol and calcium on nondriven action potentials (Fig. 3 and 4). Effects of verapamil were examined on seven preparations including four from the "irregular group." In all preparations, verapamil at 1.0×10^{-5} *M* produced a progressive decrease in amplitude and $\dot{V}_{max}$ of action potentials; and finally, all activity ceased without significant change in the resting potential (Fig. 3A). A rapid disappearance of additional depolarizations occurred invariably in preparations belonging to the "irregular group."

Representative results after the superfusion with isoproterenol at 2.0 × 10^{-6} M are shown in Figure 3B. In five

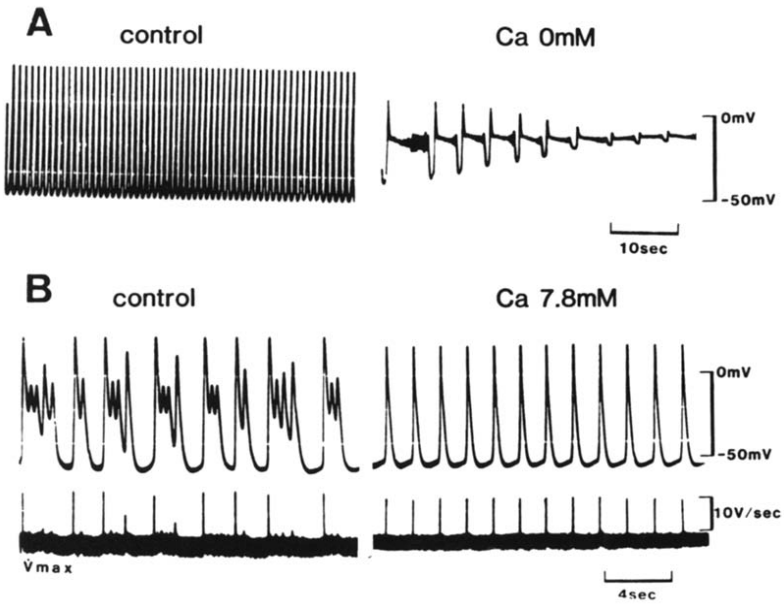

Figure 4. Effects of calcium-free and high calcium solutions. A, *Control*: Action potentials due to abnormal automaticity in control solution. *Ca O mM*: effects of calcium-free solution. Action potentials gradually slow in frequency and tend to disappear. B, *Control*: Action potentials and $\dot{V}_{max}$ in which multiple additional depolarizations constantly appeared in control solution (a preparation belonging to the "irregular group"). *Ca 7.8 mM*: effects of high calcium (7.8 m*M*) solution. In high calcium solution all additional depolarizations promptly disappeared.

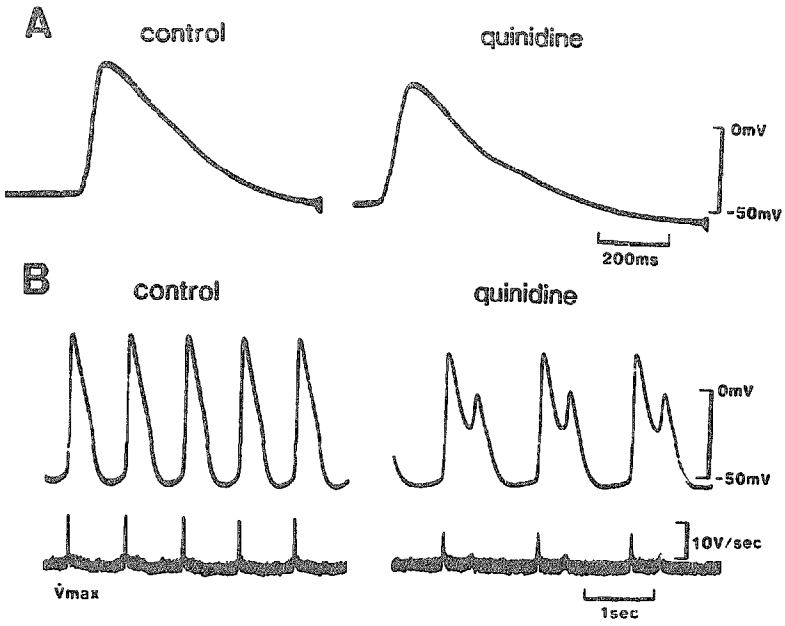

Figure 5. Effects of quinidine on nondriven potentials. A, *Control*: An action potential due to abnormal automaticity is recorded in control solution. *Quinidine*: An action potential recorded 90 min after the initiation of quinidine at 1.0×10^{-5} *M*. Note the marked prolongation in the later phase of repolarization. B, *Control*: Action potentials and $\dot{V}_{max}$ in control solution recorded from a preparation belonging to the "regular group" (different preparation). *Quinidine*: 90 min after the initiation of quinidine at 1.0×10^{-5} *M*. In this preparation, a single additional depolarization developed consistently on all action potentials giving the action potential a biphasic configuration.

preparations, isoproterenol consistently produced marked increase in amplitude and $\dot{V}_{max}$ of the action potential as well as in the firing frequently. There was only slight hyperpolarization of the maximal diastolic potential.

In Tyrode's solution devoid of calcium, all four preparations developed membrane oscillations appearing around −10 mV to −20 mV (Fig. 4A). High calcium concentration (7.8 m*M*) in four preparations from the "regular group" caused only negligible change in the action potential amplitude ($\dot{V}_{max}$), the maximal diastolic potential and the spontaneous firing frequency. The most striking change produced by high calcium concentration was a shortening of the duration of an action potential. The action potential duration measured at −40 mV decreased from 342.0 ± 13.5 to 262.1 ± 11.8 ms, by 23.3 ± 3.2% ($p < 0.01$). In four other preparations belonging to the "irregular group," high calcium solution promptly abolished observed additional depolarizations (Fig. 4B).

Effects of quinidine on nondriven action potentials (Fig. 5). Effects of quinidine were determined 90 min after the initiation of a superfusate containing quinidine at 1.0×10^{-5} *M*. Experiments were performed on eight preparations belonging to the "regular group." Quinidine caused significant increase in the action potential duration (Fig. 5A). A single additional depolarization frequently developed from the prolonged repolarization phase of an action potential giving the action potential a biphasic configuration. In two preparations, such a single additional depolarization appeared constantly on all action potentials (Fig. 5B); these two preparations were excluded from the measurement of membrane potentials.

Results from six other preparations are summarized in Table 2. Quinidine exhibited mild suppressant effects. Compared with the control value, the action potential amplitude decreased by 6.9 ± 1.8% ($p < 0.01$), $\dot{V}_{max}$ decreased by 15.7 ± 4.0% ($p < 0.05$) and the spontaneous firing frequency decreased by 18.5 ± 2.1% ($p < 0.01$). There was no significant change in the maximal diastolic potential.

Effects of amiodarone on nondriven action potentials (Fig. 6). Effects of amiodarone were determined 90 min after the initiation of a superfusate containing amiodarone at 5.0×10^{-5} *M*. Eight experiments were carried out on preparations belonging to the "regular group" (Fig. 6A, Table 3). Amiodarone demonstrated marked suppressant effects. Compared with the control value, the action potential amplitude decreased by 23.4 ± 3.6% ($p < 0.01$); $\dot{V}_{max}$ decreased by

Table 2. Effects of Quinidine on Action Potentials Due to Abnormal Automaticity

	MDP (−mV)	AMP (mV)	$\dot{V}_{max}$ (V/s)	APD_{-40} (ms)	Frequency (beats/min)
Control	56.2 ± 1.7	75.6 ± 2.5	13.3 ± 1.3	375.1 ± 25.9	60.0 ± 5.2
Quinidine	56.2 ± 1.6	70.3 ± 2.9*	11.1 ± 0.9†	450.6 ± 37.9*	48.8 ± 4.0*
% change	0.8 ± 2.3	−6.9 ± 1.8	−15.7 ± 4.0	19.1 ± 5.9	−18.5 ± 2.1

*$p < 0.01$; †$p < 0.05$. Values are mean ± SEM (n = 6). Abbreviations as in Table 1.

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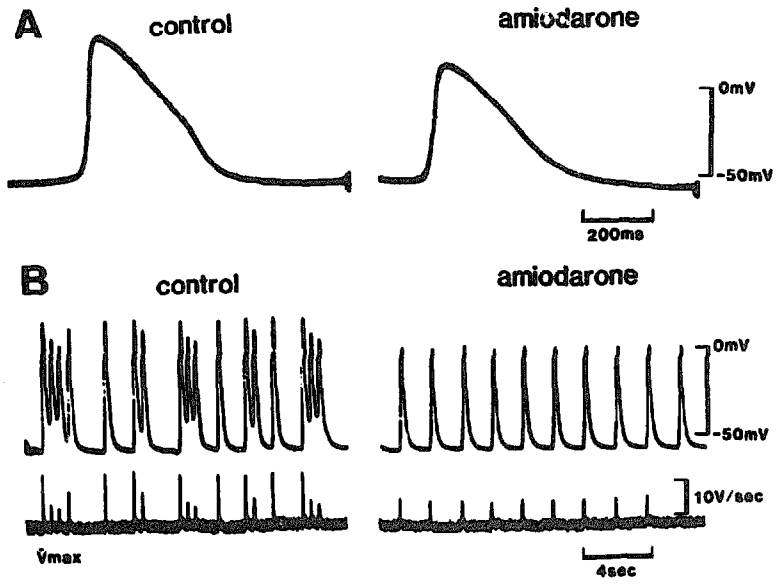

Figure 6. Effects of amiodarone on nondriven potentials. A, *Control*: An action potential due to abnormal automaticity recorded in control solution. *Amiodarone*: An action potential recorded 90 min after the initiation of amiodarone at 5.0×10^{-5} *M*. There was no significant change in the action potential duration, although its amplitude decreased considerably. B, *Control*: Action potentials and $\dot{V}_{max}$ in control solution recorded from a preparation belonging to the "irregular group." *Amiodarone*: 90 min after the initiation of amiodarone at 5.0×10^{-5} *M*. Amiodarone totally precluded the development of additional depolarizations.

44.6 ± 3.9% ($p < 0.01$) and the spontaneous firing frequency decreased by 41.9 ± 5.1% ($p < 0.01$). There was no significant change in the maximal diastolic potential or in the action potential duration measured at −40 mV. A moderate recovery in the action potential amplitude and $\dot{V}_{max}$ was observed after a washout for 30 min with Tyrode's solution containing the same concentration of bovine albumin. In contrast, reduced firing frequency did not recover after drug washout.

Six additional experiments were performed on preparations belonging to the "irregular group" to determine the effects of amiodarone on the development of triggered potentials from low membrane potential (Fig. 6B). In all preparations, the drug was uniformly effective in preventing the development of additional depolarizations. The disappearance of additional depolarizations occurred in 90 min without measurable change in the action potential duration.

Discussion

Types of triggered activity. Two types of triggered activity due to early afterdepolarizations are induced by cesium (6) or quinidine (3) in isolated cardiac tissues. The first type consists of triggered potentials from low membrane potential (−20 to −40 mV) having low amplitude or an oscillatory nature. The other arises from a higher membrane potential (−50 to −60 mV) and often gives rise to sustained rhythmic activity in the form of abnormal automaticity. In the present study, we found similar triggered activity in canine Purkinje fibers during the early phase of barium superfusion. In our model, not only was there stable firing of action potentials due to abnormal automaticity comparable with the sustained triggered activity from early afterdepolarization at high membrane potential, but also there was a consistent appearance of additional depolarizations identical to triggered potentials from early afterdepolarization at low membrane potential. This model enabled the study of the direct effects of various interventions on these two types of triggered activity independent of their secondary effects through the influence on the action potential from the normal resting potential.

Early afterdepolarizations in vitro and in torsade de pointes. Clinical experience indicates that torsade de pointes almost invariably occurs in the setting of prolonged

Table 3. Effects of Amiodarone on Action Potentials Due to Abnormal Automaticity

	MDP (−mV)	AMP (mV)	$\dot{V}_{max}$ (V/s)	APD (ms^{-40})	Frequency (beats/min)
Control	55.2 ± 1.1	78.8 ± 2.9	13.2 ± 1.1	370 ± 18.2	62.3 ± 4.0
Amiodarone	55.4 ± 1.2	60.0 ± 2.7*	7.3 ± 0.8*	340.0 ± 21.9	35.5 ± 2.8*
% change	1.0 ± 1.7	−23.4 ± 3.6	−44.6 ± 3.9	−7.9 ± 4.8	−41.9 ± 5.1
Washout	55.0 ± 1.2	72.1 ± 2.5*‡	11.6 ± 0.8†‡	353.3 ± 17.2	42.3 ± 3.6‡ns
% change	−0.7 ± 1.3	−8.3 ± 2.0	−10.5 ± 3.6	−4.4 ± 2.1	−31.0 ± 6.5

*$p < 0.01$, †$p < 0.05$ compared with control: ‡$p < 0.01$. ns = statistically not significant compared with the values in the presence of amiodarone. Values are mean ± SEM (n = 8). Abbreviations as in Table 1.

cardiac repolarization. The tendency for it to develop is usually aggravated by bradycardia and by electrolyte disturbance, especially hypokalemia. In the present study, a prolongation of the repolarization phase was often observed before the development of triggered potentials from lower membrane potential. For instance, quinidine frequently facilitated the development of the additional depolarization by prolonging the action potential duration. On the other hand, shortening of the repolarization time by a high calcium solution promptly abolished additional depolarizations. These findings indicate that such depolarizations were triggered by a longer exposure of cardiac fibers to a less negative potential at the plateau level. Therefore, the overall findings suggest that prolongation of the plateau phase of the action potential is critical to the development of this type of triggered potential as a possible arrhythmogenic mechanism.

Early afterdepolarizations with high amplitude and repetitive action potentials from a higher membrane potential may also be crucial in inducing torsade de pointes (2,6,16). As suggested by Cranefield (8), an early afterdepolarization in this voltage range develops on the basis of "two levels of resting potential" due to the N-shaped current voltage relation of the background current in the cardiac tissue (17). An important role of sodium "window" current in maintaining the depolarized level of resting potential has been also indicated (18,19). Consequently, interventions that may shift the net steady current in the inward direction are crucial in producing this form of early afterdepolarization. Therefore, low potassium concentration, by reducing potassium conductance (20), and bradycardia, by deactivating the electrogenic sodium-potassium pump (21), are likely to contribute to the development of an early afterdepolarization. Conversely, drugs such as lidocaine, which block inward sodium currents in the plateau phase (22–24), may be expected to inhibit its development.

It is noteworthy that the inhibitory action on the plateau phase inward sodium currents is not striking in the case of quinidine. On the contrary, the drug has been reported to block time-dependent outward potassium current (22,23,25). In the present study, we found that quinidine significantly prolonged the late repolarization of an action potential. Therefore, quinidine has the potential to produce an inward shift of the net steady current, an arrhythmogenic action that facilitates the development of an early afterdepolarization. Indeed, quinidine sometimes produces a depolarized level of resting potential in the presence of low potassium concentration (3).

Triggered potentials and slow calcium channel activity. Barium produces a marked prolongation of the repolarization time as a result of relatively specific inhibition of outward potassium currents; a solution of 5 m*M* barium may completely block instantaneous potassium current, thereby producing a stable depolarization of the resting potential to a voltage range where early afterdepolarizations at high membrane potential or the depolarized level of resting potential appears (26,27). In this context, the significance of the essential role of the slow calcium channel in the development of action potentials from the depolarized membrane potential should be emphasized (16,28). Our data confirm and extend previous observations. Such potentials were easily abolished by verapamil, although they were markedly augmented in amplitude with a greater $\dot{V}_{max}$ by isoproterenol. These action potentials ceased in the calcium-free solution, indicating their dependence on calcium ion as a charge carrier; this finding may partially explain the low incidence of torsade de pointes in the setting of prolonged repolarization produced by hypocalcemia (17). Barium itself has been reported to enhance the slow inward calcium current (13,29). However, it is important to distinguish the mechanism for the spontaneous (regenerative) firing of action potentials separately from the ion channel responsible for the upstroke of such action potentials.

The involvement of various currents such as the slow inward current (13), time-dependent potassium current (17) and T-type calcium channel (14,30) as potential mechanisms have all been suggested. The possibility of the participation of the transient inward current also cannot be excluded. In regard to the triggered potentials from a lower membrane potential, January et al. (31) from their study using the L-type calcium channel agonist Bay K 8644 recently proposed a repriming of L-type calcium channels: i.e., recovery from inactivation followed by reactivation due to a large "window" of this current, as a cellular mechanism for the development of such depolarizations. In the current study, we found the same voltage dependency in the case of additional depolarizations in their appearance and amplitude.

Amiodarone and torsade de pointes. The clinical observation that amiodarone rarely produces torsade de pointes in humans (32,33) despite its known propensity to markedly lengthen the QT interval beyond 600 ms (34) and to consistently produce significant bradycardia (32,33) is of particular interest. In the present study, amiodarone exhibited pronounced suppressant effects on action potentials due to abnormal automaticity. It also totally eliminated the development of triggered potentials from a lower membrane potential without shortening the action potential duration. The observed effects were similar to those found with calcium channel blockade with verapamil. Mason et al. (35) showed that amiodarone administration suppressed the development of electrically induced repetitive depolarizations from depolarized membrane potential in guinea pig ventricular muscle; Ohta et al. (36) reported that chronically administered amiodarone was more effective than acutely superfused amiodarone in attenuating triggered automaticity in rabbit cardiac muscle. These data are consistent with our findings on barium-induced action potentials, a model of triggered potentials from early afterdepolarizations.

The present study raises the possibility that the unexpectedly low incidence of clinically occurring torsade de pointes seen with amiodarone may be related at least in part to its direct suppressant effects on triggered activity from depolarized membrane potentials; these effects are most likely mediated by an inhibitory action on the slow calcium channel. Nattel et al. (37) reported a significant suppressant effect of amiodarone on slow channel potentials induced by high concentrations of external potassium and isoproterenol in canine Purkinje fibers. In the rabbit sinus node preparations, other investigators (38,39) found a marked reduction in the amplitude of the action potentials associated with the depression of phase 4 depolarization. These findings are in line with our observation, suggesting the associated calcium channel blocking action as an intrinsic property of the amiodarone molecule contributing to the drug's inhibitory effects on triggered activity in Purkinje fibers superfused with barium.

Clinical implications of the study. Our finding that amiodarone, unlike other class III agents, has a marked suppressant effect on the development of calcium channel-dependent action potentials in vitro should be emphasized. If the observed low incidence of amiodarone-induced torsade de pointes, despite this drug's primary action of markedly prolonging repolarization and producing significant bradycardia, is shown to be caused by the associated calcium channel blocking action, the addition of calcium antagonists to regimens of class III agents may prove effective in preventing and controlling torsade de pointes. These data may also be of theoretical importance in providing a scope for structure-activity relations as a basis for developing newer potent class III antiarrhythmic compounds with a low potential for proarrhythmia in the form of torsade de pointes.

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